UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/822,306	04/12/2004	Edward B. Reilly	7349.US.P1	2602

23492 7590 06/23/2006

ROBERT DEBERARDINE
ABBOTT LABORATORIES
100 ABBOTT PARK ROAD
DEPT. 377/AP6A
ABBOTT PARK, IL 60064-6008

EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/822,306	REILLY ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,40 and 41* is/are pending in the application.

4a) Of the above claim(s) *23-39 and 42-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06.06.2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-22, 40 and 41, in the reply of April 24th 2006 is acknowledged.

2. Claims 23-39 and 42-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply on April 24th 2006.

3. Claims 1-22, 40 and 41 are under examination.

Priority

4. The examiner acknowledges the statement filed on 10/04/2004, where the applicant states that the instant application is a continuation in part of U.S. patent application SEQ NO. 10/821,491 filed on April 9th, 2004; the U.S. patent application SEQ NO. 10/821,491 "SYSTEM AND METHOD FOR MINIMIZING INCREASES IN VIA RESISTANCE BY APPLYING A NITROGEN PLASMA AFTER A TITANIUM LINER DEPOSITION" and does note appear to be the same or similar subject matter as of the instant application. Hence the instant application is granted the priority date of 04/12/2004, which is the filing date of the instant application.

The applicant is requested to amend the first line if the specification appropriately.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-21, 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are not clear because claim 1 recites "..... that activates an endogenous activity of said human EpoR ....", because the exact meaning of "endogenous activity" is not clear. What activity is the applicant referring to? Specification discloses that the biological properties of EpoR include but are not limited to survival, differentiation and proliferation of hematopoeititic cells, an increase in red blood cell production and increase in hematocrit in vivo (page 14 lines 7-12 in particular), hence it is not clear as what activity is being referred to in the claim. Further, and 8-12, does the activation of the endogenous activity depend on the Koff rate as claimed in claims 1-4 or the Kd as claimed in claims 1-4. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For the purposes of this rejection the endogenous activity is considered to be stimulation of differentiation of receptor-bearing cells.

Further, it is not clear as to if the antibody of claim 22 consisting of SEQ ID NO:19-26 as a CHR2 of the heavy chain variable sequence; hence an amendment of

the claim to recite "an isolated antibody or antigen-binding fragment thereof....." would satisfy the claim language.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 14-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or antibody or antigen binding portion that specifically bind to and activate human erythropoietin receptor (EpoR) to result in the stimulation of differentiation wherein the antibody or the antigen binding fragment thereof consists of a light chain variable region as set forth in SEQ ID NO:17; and any of the heavy chain variable regions sequences as set forth in SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 and SEQ ID NO:14 – which heavy chain sequences comprise the CDR2 sequence as set forth in SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26 respectively (please see figures 7 and 8, in addition to page 45: Table4 of the instant specification for a clear description), does not reasonably provide enablement for any an antibody or antibody or antigen binding portion thereof comprising any heavy chain sequence comprising an amino acid sequence for CDR2 as selected from Y-I-X.sub.1-X.sub.2-X.sub.3-G-S-T-N-Y-N-P-S-L-K-S wherein X1, X2, and X3 can be any other combinations other than those mentioned in SEQ ID NOS:19-26; combined with any light chain sequence. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 14-21 are drawn to an antibody or antigen-binding portion thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal comprising a heavy chain variable region (HCVR) comprising an amino acid sequence of Formula I: Y-I-X.sub.1-X.sub.2-X.sub.3-G-S-T-N-Y-N-P-S-L-K-S (SEQ ID NO:18) wherein: X.sub.1 is independently selected from the group consisting of tyrosine (Y), glycine (G) and alanine (A); X.sub.2 is independently selected from the group consisting of tyrosine (Y), glycine (G), alanine (A), glutamine (E) and aspartic acid (D); and X.sub.3 is independently selected from the group consisting of serine (S), glycine (G), glutamine (E) and threonine (T) with the proviso that X1-X2-X3 is other than Y-Y-S, wherein X.sub.1 is G and X.sub.2 and X.sub.3 are as defined therein, wherein X.sub.2 is G and X.sub.1 and X.sub.3 are as defined therein, wherein X.sub.3 is E and X.sub.1 and X.sub.2 are as defined therein, wherein X.sub.1 is G, X.sub.2 is G and X.sub.3 is as defined therein, wherein X.sub.1 is as defined therein, X.sub.2 is G and X.sub.3 is E, wherein X.sub.1 is G, X.sub.2 is G and X.sub.3 is E, wherein X.sub.1 is A, X.sub.2 is G and X.sub.3 is T, which presents the possibility of vary many combinations within the sequence, all of which are not described in the specification and hence it is impossible to interpret that all the combinations of X.sub.1-X.sub.2-X.sub.3 can form a functional antibody or antibody antigen binging portion thereof. In addition, the specification does not disclose any antibody or antigen-binding portion thereof that activates an

endogenous activity of a human erythropoietin receptor wherein only one CDR is defined as an amino acid sequence selected from the group consisting of (a) YIGGEGSTNYNPSLKS (SEQ ID NO:19); (b) YIAGTGSTNYNPSLKS (SEQ ID NO:20); (c) YIGYSGSTNYNPSLKS (SEQ ID NO:21); (d) YIYGSGSTNYNPSLKS (SEQ ID NO:22); (e) YIYYEGSTNYNPSLKS (SEQ ID NO:23); (f) YIGGSGSTNYNPSLKS (SEQ ID NO:24); (g) YIYGEGSTNYNPSLKS (SEQ ID NO:25); and (h) YIGYEGSTNYNPSLKS (SEQ ID NO:26).

The specification teaches an antibody or antibody or antigen binding portion that specifically bind to and activate human erythropoietin receptor (EpoR) to result in the stimulation of differentiation wherein the antibody or the antigen binding fragment thereof consists of a light chain variable region as set forth in SEQ ID NO:17; and any of the heavy chain variable regions sequences as set forth in SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 and SEQ ID NO:14 – which heavy chain sequences comprise the CDR2 sequence as set forth in SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25 and SEQ ID NO:26 respectively (please see figures 7 and 8, in addition to page 45: Table4 of the instant specification for a clear description). However, the specification does not teach an antibody or antigen-binding portion thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal to result in the stimulation of differentiation comprising a CDR2 of a heavy chain variable region (HCVR) comprising an amino acid sequence of Formula I: Y-I-X.sub.1-X.sub.2-X.sub.3-G-S-T-N-Y-N-P-S-L-K-S (SEQ ID NO:18) wherein: X.sub.1 is

independently selected from the group consisting of tyrosine (Y), glycine (G) and alanine (A); X.sub.2 is independently selected from the group consisting of tyrosine (Y), glycine (G), alanine (A), glutamine (E) and aspartic acid (D); and X.sub.3 is independently selected from the group consisting of serine (S), glycine (G), glutamine (E) and threonine (T) with the proviso that X1-X2-X3 is other than Y-Y-S, wherein the combination of X.sub.1, X.sub.2 and X.sub.3 can be selected from any of X.sub.1 is G and X.sub.2 and X.sub.3 are as defined therein, wherein X.sub.2 is G and X.sub.1 and X.sub.3 are as defined therein, wherein X.sub.3 is E and X.sub.1 and X.sub.2 are as defined therein, wherein X.sub.1 is G, X.sub.2 is G and X.sub.3 is as defined therein, wherein X.sub.1 is as defined therein, X.sub.2 is G and X.sub.3 is E, wherein X.sub.1 is G, X.sub.2 is G and X.sub.3 is E, wherein X.sub.1 is A, X.sub.2 is G and X.sub.3 is T. This presents the possibility of vary many combinations for the region of X.sub.1-X.sub.2-X.sub.3 within the sequence, all of which are not described in the specification. Thus, it is impossible to interpret that all the combinations of X.sub.1-X.sub.2-X.sub.3 can form a functional antibody or antibody antigen binging portion thereof. Further, the specification does not disclose any antibody or antigen-binding portion thereof that activates an endogenous activity of a human erythropoietin receptor wherein only one CDR is defined as an amino acid sequence selected from the group consisting of (a) YIGGEGSTNYNPSLKS (SEQ ID NO:19); (b) YIAGTGSTNYNPSLKS (SEQ ID NO:20); (c) YIGYSGSTNYNPSLKS (SEQ ID NO:21); (d) YIYGSGSTNYNPSLKS (SEQ ID NO:22); (e) YIYYEGSTNYNPSLKS (SEQ ID NO:23); (f) YIGGSGSTNYNPSLKS (SEQ ID NO:24); (g) YIYGEGSTNYNPSLKS (SEQ ID NO:25); and (h) YIGYEGSTNYNPSLKS

(SEQ ID NO:26), and no other corresponding light chain variable sequences that are specific such that the binds to EpoR and activates the human erythropoietin receptor (EpoR) to result in the stimulation of differentiation

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Even if one has the correct amino acid sequence, a skilled practitioner would not be able to predict the level of expression of the resulting

synthetic DNA sequence For example, the cellular location of the Int-2 oncoprotein is determined by the choice of initiation codon, i.e., either the AUG coding for methionine or CUG coding for leucine. AUG-initiated Int-2 proteins are secreted from the cells, while CUG-initiated Int-2 proteins are localized to the cell nucleus. Acland et al., Nature Vol 343:662-665 (1990).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lin et al and Acland et al conclusively demonstrate.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the

result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 6, 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliot (US Patent 6319499, Date Filed June 5, 1998; IDS: 01/06/2005) as evidenced by the specification.

Claims 1-4 and 6 are interpreted to be an isolated antibody, or an antigen-binding portion thereof, that dissociates from human erythropoietin receptor (EpoR) with a K.sub.off rate constant of greater than about 1.3.times.10.sup.-3 s.sup.-1 and that activates an endogenous activity of said human EpoR in a mammal to result in the

stimulation of differentiation of receptor-bearing cells, wherein said K.sub.off rate constant is about 1.4.times.10.sup.-3 s.sup.-1 or greater, wherein said K.sub.off rate constant is about 1.9.times.10.sup.-3 s.sup.-1, wherein said K.sub.off rate constant is about 4.8.times.10.sup.-3 s.sup.-1 and wherein said antibody is a monoclonal antibody. Claims 8-13 are interpreted as the said antibody that binds to human EpoR with a K.sub.d of about 7 nM or greater, wherein said K.sub.d is about 8.5 nM or greater, wherein said K.sub.d is about 20 nM, wherein said K.sub.d is about 32 nM, wherein said K.sub.d is about 7-32 nM inclusive and wherein the antibody or antigen-binding portion thereof of claim 1 which is a human antibody.

Elliot teaches an antibody or fragment thereof which activates an erythrotpoietin receptor, wherein the activation of an EPO receptor" denotes one or more molecular processes which an EPO receptor undergoes that result in transduction of a signal to the interior of a receptor-bearing cell, wherein the signal ultimately brings about one or more changes in cellular physiology. Cellular responses to EPO receptor activation are typically changes in the proliferation or differentation of receptor-bearing cells (paragraph 3 in particular), including stimulation of proliferation, stimulation of differentiation and inhibition of apoptosis (paragraph 8). Elliot al teaches that EPO receptors of the invention will preferably be mammalian EPO receptors and, in a particularly preferred embodiment, will be human EPO receptor (paragraph 4, n particular). Elliot also teaches monoclonal antibodies and fragments thereof that encompass those fragments which activate an EPO receptor, in addition to humanized

antibodies, and fully human antibodies (paragraph 6, in particular).

Thus, Elliot clearly teaches an antibody or fragment thereof which activates an erythrotpoietin receptor, wherein the activation of an EPO receptor resulting in the stimulation of differentiation of receptor-bearing cells. Elliot also teaches that the the activation of erythropoietin receptor is also involved in changes in the proliferation or differentation of receptor-bearing cells, including stimulation of proliferation, stimulation of differentiation and inhibition of apoptosis, and as evidenced by the specification the activation of the endogenous activity of the human EpoR can lead to different biological properties but are not limited to survival, differentiation and proliferation of hematopoeititic cells, an increase in red blood cell production and increase in hematocrit in vivo.

Elliot is silence as to the Koff and Kd of the antibody, however, since Elliot's antibody binds the same antigen and has the same function as claimed, it is the examiner's position that Elliot have produced the antibody or fragment thereof that exhibit various Koff rate constant as claimed in claims 1-4 and the various Kd values as claimed in claims 8-12. One of ordinary skill in the art would reasonably conclude that Elliot's antibody also possesses the same structural and functional properties as those of the antibodies claimed, and, therefore, it appears that Elliot have produced the antibody that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed Koff and Kd values of the antibody of Elliot, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the

claimed antibody and and antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, claims 1-4, 6, 8-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Elliot as evidenced by the specification.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1-4, 6 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elliot (US Patent 6319499, Date Filed June 5, 1998; IDS:

01/06/2005) in view of Schier et al (J. Mol. Biol. 1996. 263:551-567) and further in view of Lowman et al (PGPUB 200300224397; Date filed February 11, 2003).

Claims 1-4, 6 and 8-13 have been described supra. Further, claim 5 is drawn to the antibody or antigen-binding fragment portion of claim 1 wherein said Koff rate constant is determined by surface plasmon resonance.

Elliot has been described supra. Elliot et al does not teach the Koff and Kd rate of the antibody or antigen binding fragment and that the Koff rate constant is determined by surface plasmon resonance.

Schier et al teach a method of randomizing or mutating the CDR3 regions of the variable light and heavy chains that produced picomolar affinity. The method of Shier et al comprises sequentially mutating (i.e. modifying) CDR3 of the variable light chain and variable heavy chain, obtaining mutated antibodies by selection and purification, determining the Koff rate constants using the BIAcore biosensor and the mutated antibodies has an affinity ranging from 1.3×10^{-3} s^{-1} to 6.3×10^{-3} s^{-1} as recited in claims 1-4 (please see tables 2 and 4, in particular). Further Schier et al teach that certain Vl and Vl-VH CDR3 mutant antibodies had dissociation rates (Kd) ranging from 4.5nm to 16.16nm (please see tables 3 and 4 in particular).

Lowman et al (PGPUB 20030224397; Date filed February 11, 2003) teach the affinity maturation process of the immune system, by introducing mutations into antibody genes in vitro and using affinity selection to isolate mutants with improved

affinity. Such mutant antibodies can be displayed on the surface of filamentous bacteriophage and antibodies can be selected by their affinity for antigen or by their kinetics of dissociation (off-rate) from antigen, wherein the "dissociation rate" refers to the off-rate constant (k.sub.-1), or breaking of short range interactions between antibody and antigen, such that the Dissociation rates were measured by surface plasmon resonance on a BIACORE-2000.RTM instrument.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced the antibody as claimed.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have used the antibody of Elliot et al, because Elliot et al teaches an antibody or fragment thereof which activates an erythrotpoietin receptor, wherein the activation of an EPO receptor" denotes one or more molecular processes which an EPO receptor undergoes that result in transduction of a signal to the interior of a receptor-bearing cell, wherein the signal ultimately brings about one or more changes in cellular physiology, in particular is stimulation of differentiation of receptor-bearing cells, and further because Elliot et al teaches that the cellular responses to EPO receptor activation are typically changes in the proliferation or differentation of receptor-bearing cells in addition that the EPO receptors of the invention will preferably be mammalian EPO receptors and, in a particularly preferred embodiment, will be human EPO receptor and further teaches monoclonal antibodies

and fragments thereof that encompass those fragments which activate an EPO receptor, in addition to humanized antibodies, and fully human antibodies.

In addition, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have used the antibody of Elliot et al and combined with the teachings of Shier et al because Schier et al teach a method of randomizing or mutating the CDR3 regions of the variable light and heavy chains that produced picomolar affinity wherein the method of Shier et al comprises sequentially mutating (i.e. modifying) CDR3 of the variable light chain and variable heavy chain, obtaining mutated antibodies by selection and purification, determining the Koff rate constants using the BIAcore biosensor and the mutated antibodies has an affinity ranging from 1.3×10^{-3} s^{-1} to 6.3×10^{-3} s^{-1} as recited in claims 1-4, in addition Schier et al teach that certain VI and VI-VH CDR3 mutant antibodies had dissociation rates (Kd) ranging from 4.5nm to 16.16nm.

Moreover, one of ordinary skill in the art would have known to determine the Koff rate constant by surface plasmon resonance, because Elliot et al teaches an antibody or fragment thereof which activates an erythrotpoietin receptor and because Lowman et al teach the affinity of the antibodies can be selected by their affinity for antigen or by their kinetics of dissociation (off-rate) from antigen, wherein the "dissociation rate" refers to the off-rate constant (k.sub.-1), or breaking of short range interactions between antibody and antigen, such that the Dissociation rates were measured by surface plasmon resonance on a BIACORE-2000.RTM instrument.

Furthermore, one of ordinary skill in the art would have known to Produce the antibody as claimed with the properties as claimed, various Koff rate constant and Kd values, because as explained above (in the 102 rejection), Elliot teaches an antibody or fragment thereof which activates an erythrotpoietin receptor wherein the "activation of an EPO receptor" denotes a result in transduction of a signal to the interior of a receptor-bearing cell, wherein the signal ultimately brings about one or more changes in cellular physiology; and one of ordinary skill in the art would expect and be motivated to calculate the Koff rate constant and the Kd values for antigen-binding property of the antibody to evaluate the result of the activation of the EPO receptor upon the binding of the antibody to the human EpoR, and because Shier et al teach a method of randomizing or mutating the CDR3 regions of the variable light and heavy chains that produced nanomolar affinity as claimed in the instant claims, and because Lowman et al teach the affinity of the antibodies can be selected by their affinity for antigen or by their kinetics of dissociation (off-rate) from antigen, wherein the "dissociation rate" refers to the off-rate constant (k.sub.-1), or breaking of short range interactions between antibody and antigen, such that the Dissociation rates were measured by surface plasmon resonance on a BIACORE-2000.RTM instrument.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

14. Claims 1-22, 40 and 41 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22, 40 and 41 of copending Application No. 11/102,424, because claims 1-22, 40 and 41 of the instant application are identical to and are of the same scope as claims 1-22, 40 and 41 of copending Application No. 11/102,424. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1-22, 40 and 41 of this application conflict with claims 1-22, 40 and 41 of Application No. 11/102,424 (PGPUB 20060018902). 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Schier et al. J. Mol. Biol. 1996. 255: 28-43.

2. Thompson et al. J. Mol. Biol. 1996. 256: 77-88.

3. Wu et al. Proc. Natl. Acad. Sci. 1998. 95:6037-6042.

4. Zeder-Lutz et al. Molecular Immunology. 1993. 30:145-155.

5. Shier and Marks. Hum. Antibod. Hybridomas. 1996. 7:97-105.

6. Duenas et al. Molecular Immunology. 1996. 33:279-285.

Conclusion

16. No claims are allowed

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER